HPS Trailer Page
for

WEST

UserID: nbasi

Printer: cm1_10e14_gbekptr

Summary

Document	Pages	Printed	Missed	Copies
WO000210393	64	64	0	1
Total (1)	64	64	0	-

nbasi

Printed by HPS Server

for

WEST

Printer: cm1_10e14_gbekptr

Date: 12/27/02

Time: 10:31:34

Document Listing

Document	Selected Pages	Page Range	Copies
US20020039763	41	1 - 41	1
Total (1)	41	-	-

L14: Entry 4 of 9 File: PGPB Jan 31, 2002

DOCUMENT-IDENTIFIER: US 20020012669 A1
TITLE: Human cytokine receptor

Summary of Invention Paragraph (12):
[0009] As described below, the present invention provides isolated polypeptides comprising an amino acid sequence that is at least 70%, at least 80%, or at least 90% identical to a reference amino acid sequence of SEQ ID NO:2 selected from the group consisting of: (a) amino acid residues amino acid residues 21 to 231, (b) amino acid residues 21 to 210, (c) amino acid residues 22 to 231, (d) amino acid residues 22 to 210, (e) amino acid residues 22 to 108, (f) amino acid residues 112 to 210, and (g) amino acid residues 21 to 110, wherein the isolated polypeptide specifically binds with an antibody that specifically binds with a polypeptide consisting of the amino acid sequence of SEQ ID NO:2. Illustrative polypeptides include polypeptides comprising either amino acid residues 22 to 231 of SEQ ID NO:2 or amino acid residues 22 to 210 of SEQ ID NO:2. Moreover, the present invention also provides isolated polypeptides as disclosed above that bind IL-TIF (e.g., human IL-TIF polypeptide sequence as shown in SEQ ID NO: 15). The human IL-TIF polynucleotide sequence is shown in SEQ ID NO: 14.

Summary of Invention Paragraph (14):
[0011] The present invention also includes variant Zcytor16 polypeptides, wherein the amino acid sequence of the variant polypeptide shares an identity with amino acid residues 22 to 210 of SEQ ID NO:2 selected from the group consisting of at least 70% identity, at least 80% identity, at least 90% identity, at least 95% identity, or greater than 95% identity, and wherein any difference between the amino acid sequence of the variant polypeptide and the corresponding amino acid sequence of SEQ ID NO:2 is due to one or more conservative amino acid substitutions. Moreover, the present invention also provides isolated polypeptides as disclosed above that bind IL-TIF.

Summary of Invention Paragraph (16):
[0013] The present invention also provides isolated nucleic acid molecules that encode a Zcytor16 polypeptide, wherein the nucleic acid molecule is selected from the group consisting of: (a) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:3, (b) a nucleic acid molecule encoding an amino acid sequence that comprises either amino acid residues 22 to 231 of SEQ ID NO:2 or amino acid residues 22 to 210 of SEQ ID NO:2, and (c) a nucleic acid molecule that remains hybridized following stringent wash conditions to a nucleic acid molecule comprising the nucleotide sequence of nucleotides 64 to 630 of SEQ ID NO: 1, or the complement of the nucleotide sequence of nucleotides 64 to 630 of SEQ ID NO: 1. Illustrative nucleic acid molecules include those in which any difference between the amino acid sequence encoded by nucleic acid molecule (c) and the corresponding amino acid sequence of SEQ ID NO:2 is due to a conservative amino acid substitution. The present invention further contemplates isolated nucleic acid molecules that comprise nucleotides 64 to 630 of SEQ ID NO:1. Moreover, the present invention also provides isolated polynucleotides that encode polypeptides as disclosed above that bind IL-TIF.

Summary of Invention Paragraph (25):
[0022] The present invention also provides monomeric, homodimeric, heterodimeric and multimeric receptors comprising a zcytor16 extracellular domain. Such receptors are soluble or membrane bound, and act as antagonists of the zcytor16 ligand, IL-TIF (e.g., the human IL-TIF as shown in SEQ ID NO:15). In a preferred embodiment, such receptors are soluble receptors comprising at least one zcytor16 extracellular domain

polypeptide comprising amino acids 22-231, or 22-210 of SEQ ID NO:2. The present invention further includes isolated nucleic acid molecules that encode such receptor polypeptides.

Summary of Invention Paragraph (26):
[0023] The present invention also provides polyclonal and monoclonal antibodies to monomeric, homodimeric, heterodimeric and multimeric receptors comprising a zcytor16 extracellular domain such as those described above. Moreover, such antibodies can be used antagonize the binding to the zcytor16 ligand, IL-TIF (SEQ ID NO:15), to the zcytor16 receptor.

Summary of Invention Paragraph (86):
[0083] Regardless of the particular method used to identify a variant Zcytor16 gene or variant Zcytor16 polypeptide, a variant gene or polypeptide encoded by a variant gene may be functionally characterized the ability to bind specifically to an anti-Zcytor16 antibody. A variant Zcytor16 gene or variant Zcytor16 polypeptide may also be functionally characterized the ability to bind to its ligand, IL-TIF, using a biological or biochemical assay described herein.

Summary of Invention Paragraph (142):
[0139] Although sequence analysis can be used to further define the Zcytor16 ligand binding region, amino acids that play a role in Zcytor16 binding activity (such as binding of zcytor16 to ligand IL-TIF, or to an anti-zcytor16 antibody) can also be determined by physical analysis of structure, as determined by such techniques as nuclear magnetic resonance, crystallography, electron diffraction or photoaffinity labeling, in conjunction with mutation of putative contact site amino acids. See, for example, de Vos et al., Science 255:306 (1992), Smith et al., J. Mol. Biol. 224:899 (1992), and Wlodaver et al., FEBS Lett. 309:59 (1992).

Summary of Invention Paragraph (182):
[0179] Moreover, zcytor16 polypeptides can be expressed as monomers, homodimers, heterodimers, or multimers within higher eukaryotic cells. Such cells can be used to produce zcytor16 monomeric, homodimeric, heterodimeric and multimeric receptor polypeptides that comprise at least one zcytor16 polypeptide ("zcytor16-comprising receptors" or "zcytor16-comprising receptor polypeptides"), or can be used as assay cells in screening systems. Within one aspect of the present invention, a polypeptide of the present invention comprising the zcytor16 extracellular domain is produced by a cultured cell, and the cell is used to screen for ligands for the receptor, including the natural ligand, IL-TIF, as well as agonists and antagonists of the natural ligand. To summarize this approach, a cDNA or gene encoding the receptor is combined with other genetic elements required for its expression (e.g., a transcription promoter), and the resulting expression vector is inserted into a host cell. Cells that express the DNA and produce functional receptor are selected and used within a variety of screening systems. Each component of the monomeric, homodimeric, heterodimeric and multimeric receptor complex can be expressed in the same cell. Moreover, the components of the monomeric, homodimeric, heterodimeric and multimeric receptor complex can also be fused to a transmembrane domain or other membrane fusion moiety to allow complex assembly and screening of transfectants as described above.

Summary of Invention Paragraph (184):
[0181] Suitable host cells can be engineered to produce the necessary receptor subunits or other cellular component needed for the desired cellular response. This approach is advantageous because cell lines can be engineered to express receptor subunits from any species, thereby overcoming potential limitations arising from species specificity. Species orthologs of the human receptor cDNA can be cloned and used within cell lines from the same species, such as a mouse cDNA in the BaF3 cell line. Cell lines that are dependent upon one hematopoietic growth factor, such as GM-CSF or IL-3, can thus be engineered to become dependent upon another cytokine that acts through the zcytor16 receptor, such as IL-TIF.

Summary of Invention Paragraph (186):
[0183] A natural ligand for the Zcytor16 receptor can also be identified by mutagenizing a cell line expressing the full-length receptor or receptor fusion (e.g., comprising the zcytor16 extracellular domain fused to the transmembrane and signaling domain of another cytokine receptor) and culturing it under conditions that select for

autocrine growth. See WIPO publication WO 95/21930. Within a typical procedure, IL-3 dependent BaF3 cells expressing Zcytor16 and the necessary additional subunits are mutagenized, such as with 2-ethylmethanesulfonate (EMS). The cells are then allowed to recover in the presence of IL-3, then transferred to a culture medium lacking IL-3 and IL-4. Surviving cells are screened for the production of a zcytor16 ligand (e.g., IL-TIF), such as by adding soluble receptor to the culture medium or by assaying conditioned media on wild-type BaF3 cells and BaF3 cells expressing the receptor. Using this method, cells and tissues expressing IL-TIF can be identified.

Summary of Invention Paragraph (187):
[0184] Moreover several IL-TIF responsive cell lines are known (Dumontier et al., J. Immunol. 164:1814-1819, 2000; Dumoutier, L. et al., Proc. Nat'l. Acad. Sci. 97:10144-10149, 2000; Xie MH et al., J. Biol. Chem. 275: 31335-31339, 2000; Kotenko SV et al., JBC in press), as well as those that express the IL-TIF receptor subunit zcytor11. For example, the following cells are responsive to IL-TIF: TK-10 (Xie MH et al., supra.) (human renal carcinoma); SW480 (ATCC No. CCL-228) (human colon adenocarcinoma); HepG2 (ATCC No. HB-8065) (human hepatoma); PC12 (ATCC No. CRL-1721) (murine neuronal cell model; rat pheochromocytoma); and MES13 (ATCC No. CRL-1927) (murine kidney mesangial cell line). In addition, some cell lines express zcytor11 (IL-TIF receptor) are also candidates for responsive cell lines to IL-TIF: A549 (ATCC No. CCL-185) (human lung carcinoma); G-361 (ATCC No. CRL-1424) (human melanoma); and Caki-1 (ATCC No. HTB-46) (human renal carcinoma). These cells can be used in assays to assess the functionality of zcytor16 as an IL-TIF antagonist or anti-inflammatory factor.

Summary of Invention Paragraph (189):
[0186] A second class of hybrid receptor polypeptides comprise the extracellular (ligand-binding) domain of Zcytor16 (approximately residues 22 to 231 of SEQ ID NO:2; SEQ ID NO:13) with an intracellular domain of a second receptor, preferably a hematopoietic cytokine receptor, and a transmembrane domain. Hybrid zacytor11 monomers, homodimers, heterodimers and multimers of the present invention receptors of this second class are expressed in cells known to be capable of responding to signals transduced by the second receptor. Together, these two classes of hybrid receptors enable the identification of a responsive cell type for the development of an assay for detecting IL-TIF. Moreover, such cells can be used in the presence of IL-TIF to assay the soluble receptor antagonists of the present invention in a competition-type assay. In such assay, a decrease in the proliferation or signal transduction activity of IL-TIF in the presence of a soluble receptor of the present invention demonstrates antagonistic activity. Moreover IL-TIF-soluble receptor binding assays can also be used to assess whether a soluble receptor antagonizes IL-TIF activity.

Summary of Invention Paragraph (198):
[0195] The present invention further provides a variety of other polypeptide fusions and related multimeric proteins comprising one or more polypeptide fusions. For example, a soluble zcytor16 receptor or soluble zcytor16 heterodimeric polypeptide, such as soluble zcytor16/CRF2-4, can be prepared as a fusion to a dimerizing protein as disclosed in U.S. Pat. Nos. 5,155,027 and 5,567,584. Preferred dimerizing proteins in this regard include immunoglobulin constant region domains, e.g., IgG.kappa.1, and the human .kappa. light chain. Immunoglobulin-soluble zcytor16 receptor or immunoglobulin-soluble zcytor16 heterodimeric or multimeric polypeptide, such as immunoglobulin-soluble zcytor16/CRF2-4 fusions can be expressed in genetically engineered cells to produce a variety of multimeric zcytor16 receptor analogs. Auxiliary domains can be fused to soluble zcytor16 receptor or soluble zcytor16 heterodimeric or multimeric polypeptides, such as soluble zcytor16/CRF2-4 to target them to specific cells, tissues, or macromolecules (e.g., collagen, or cells expressing the zcytor16 ligand, IL-TIF). A zcytor16 polypeptide can be fused to two or more moieties, such as an affinity tag for purification and a targeting domain. Polypeptide fusions can also comprise one or more cleavage sites, particularly between domains. See, Tuan et al., Connective Tissue Research 34:1-9, 1996.

Summary of Invention Paragraph (208):
[0205] Zcytor16 polypeptides can be used to identify and to isolate Zcytor16 ligands. For example, proteins and peptides of the present invention can be immobilized on a column and used to bind ligands from a biological sample that is run over the column (Hermanson et al. (eds.), Immobilized Affinity Ligand Techniques, pages 195-202

(Academic Press 1992)). As such, zcytor16 polypeptides of the present invention can be used to identify and isolate IL-TIF for either diagnostic, or production purposes.

Summary of Invention Paragraph (210):
[0207] For example, the microphysiometer is used to measure responses of an Zcytor16-expressing eukaryotic cell, compared to a control eukaryotic cell that does not express Zcytor16 polypeptide. Suitable cells responsive to Zcytor16-modulating stimuli include recombinant host cells comprising a Zcytor16 expression vector, and cells that naturally express Zcytor16. Extracellular acidification provides one measure for a Zcytor16-modulated cellular response. In addition, this approach can be used to identify ligands, agonists, and antagonists of Zcytor16 ligand, IL-TIF. For example, a molecule can be identified as an agonist of Zcytor16 ligand by providing cells that express a Zcytor16 polypeptide, culturing a first portion of the cells in the absence of the test compound, culturing a second portion of the cells in the presence of the test compound, and determining whether the second portion exhibits a cellular response, in comparison with the first portion.

Summary of Invention Paragraph (231):
[0228] The polypeptides of the present invention can also be isolated by exploitation of particular properties. For example, immobilized metal ion adsorption (IMAC) chromatography can be used to purify histidine-rich proteins, including those comprising polyhistidine tags. Briefly, a gel is first charged with divalent metal ions to form a chelate (Sulkowski, Trends in Biochem. 3:1 (1985)). Histidine-rich proteins will be adsorbed to this matrix with differing affinities, depending upon the metal ion used, and will be eluted by competitive elution, lowering the pH, or use of strong chelating agents. Other methods of purification include purification of glycosylated proteins by lectin affinity chromatography and ion exchange chromatography (M. Deutscher, (ed.), Meth. Enzymol. 182:529 (1990)). Within additional embodiments of the invention, a fusion of the polypeptide of interest and an affinity tag (e.g., maltose-binding protein, an immunoglobulin domain) may be constructed to facilitate purification. Moreover, the ligand-binding properties of zcytor16 extracellular domain can be exploited for purification, for example, of zcytor16-comprising soluble receptors; for example, by using affinity chromatography wherein IL-TIF ligand is bound to a column and the zcytor16-comprising receptor is bound and subsequently eluted using standard chromatography methods.

Summary of Invention Paragraph (280):
[0277] 11. Use of Anti-Zcytor16 Antibodies to Detect Zcytor16 or Antagonize Zcytor16 Binding to IL-TIF

Summary of Invention Paragraph (295):
[0292] Alternative techniques for generating or selecting antibodies useful herein include in vitro exposure of lymphocytes to soluble zcytor16 monomeric receptor or soluble zcytor16 homodimeric, heterodimeric or multimeric polypeptides, and selection of antibody display libraries in phage or similar vectors (for instance, through use of immobilized or labeled soluble zcytor16 monomeric receptor or soluble zcytor16 homodimeric, heterodimeric or multimeric polypeptides). Genes encoding polypeptides having potential binding domains such as soluble zcytor16 monomeric receptor or soluble zcytor16 homodimeric, heterodimeric or multimeric polypeptide can be obtained by screening random peptide libraries displayed on phage (phage display) or on bacteria, such as E. coli. Nucleotide sequences encoding the polypeptides can be obtained in a number of ways, such as through random mutagenesis and random polynucleotide synthesis. These random peptide display libraries can be used to screen for peptides which interact with a known target which can be a protein or polypeptide, such as a ligand or receptor, a biological or synthetic macromolecule, or organic or inorganic substances. Techniques for creating and screening such random peptide display libraries are known in the art (Ladner et al., U.S. Pat. No. 5,223,409; Ladner et al., U.S. Pat. No. 4,946,778; Ladner et al., U.S. Pat. No. 5,403,484 and Ladner et al., U.S. Pat. No. 5,571,698) and random peptide display libraries and kits for screening such libraries are available commercially, for instance from Clontech (Palo Alto, Calif.), Invitrogen Inc. (San Diego, Calif.), New England Biolabs, Inc. (Beverly, Mass.) and Pharmacia LKB Biotechnology Inc. (Piscataway, N.J.). Random peptide display libraries can be screened using the soluble zcytor16 monomeric receptor or soluble zcytor16 homodimeric, heterodimeric or multimeric polypeptide sequences disclosed herein to identify proteins which bind to zcytor16-comprising

receptor polypeptides. These "binding polypeptides," which interact with soluble zcytor16-comprising receptor polypeptides, can be used for tagging cells; for isolating homolog polypeptides by affinity purification; they can be directly or indirectly conjugated to drugs, toxins, radionuclides and the like. These binding polypeptides can also be used in analytical methods such as for screening expression libraries and neutralizing activity, e.g., for blocking interaction between IL-TIF ligand and receptor, or viral binding to a receptor. The binding polypeptides can also be used for diagnostic assays for determining circulating levels of soluble zcytor16-comprising receptor polypeptides; for detecting or quantitating soluble or non-soluble zcytor16-comprising receptors as marker of underlying pathology or disease. These binding polypeptides can also act as "antagonists" to block soluble or membrane-bound zcytor16 monomeric receptor or zcytor16 homodimeric, heterodimeric or multimeric polypeptide binding (e.g. to ligand) and signal transduction in vitro and in vivo. Again, these binding polypeptides serve as anti-zcytor16 monomeric receptor or anti-zcytor16 homodimeric, heterodimeric or multimeric polypeptides and are useful for inhibiting IL-TIF activity, as well as receptor activity or protein-binding. Antibodies raised to the natural receptor complexes of the present invention may be preferred embodiments, as they may act more specifically against the IL-TIF, or more potently than antibodies raised to only one subunit. Moreover, the antagonistic and binding activity of the antibodies of the present invention can be assayed in the IL-TIF proliferation, signal trap, luciferase or binding assays in the presence of IL-TIF and zcytor16-comprising soluble receptors, and other biological or biochemical assays described herein.

Summary of Invention Paragraph (296):
[0293] Antibodies to monomeric zcytor16 receptor or zcytor16 homodimeric, heterodimeric or multimeric zcytor16-containing receptors may be used for tagging cells that express zcytor16 receptors; for isolating soluble zcytor16-comprising receptor polypeptides by affinity purification; for diagnostic assays for determining circulating levels of soluble zcytor16-comprising receptor polypeptides; for detecting or quantitating soluble zcytor16-comprising receptors as marker of underlying pathology or disease; in analytical methods employing FACS; for screening expression libraries; for generating anti-idiotypic antibodies that can act as IL-TIF agonists; and as neutralizing antibodies or as antagonists to block zcytor16 receptor function, or to block IL-TIF activity in vitro and in vivo. Suitable direct tags or labels include radionuclides, enzymes, substrates, cofactors, biotin, inhibitors, fluorescent markers, chemiluminescent markers, magnetic particles and the like; indirect tags or labels may feature use of biotin-avidin or other complement/anti-complement pairs as intermediates. Antibodies herein may also be directly or indirectly conjugated to drugs, toxins, radionuclides and the like, and these conjugates used for in vivo diagnostic or therapeutic applications. Moreover, antibodies to soluble zcytor16-comprising receptor polypeptides, or fragments thereof may be used in vitro to detect denatured or non-denatured zcytor16-comprising receptor polypeptides or fragments thereof in assays, for example, Western Blots or other assays known in the art.

Summary of Invention Paragraph (297):
[0294] Antibodies to soluble zcytor16 receptor or soluble zcytor16 homodimeric, heterodimeric or multimeric receptor polypeptides are useful for tagging cells that express the corresponding receptors and assaying their expression levels, for affinity purification, within diagnostic assays for determining circulating levels of receptor polypeptides, analytical methods employing fluorescence-activated cell sorting. Moreover, divalent antibodies, and anti-idiotypic antibodies may be used as agonists to mimic the effect of the zcytor16 ligand, IL-TIF.

Summary of Invention Paragraph (305):
[0302] Moreover, we have shown that the zcytor16 receptor binds a ligand called T-cell inducible Factor (IL-TIF) (SEQ ID NO:15; Dumoutier, L. et al., Proc. Nat'l. Acad. Sci. 97:10144-10149, 2000; mouse IL-TIF sequence is shown in Dumontier et al., J. Immunol. 164:1814-1819, 2000). Moreover, commonly owned zcytor11 (U.S. Pat. No. 5,965,704) and CRF2-4 receptor also bind IL-TIF (See, WIPO publication WO 00/24758; Dumontier et al., J. Immunol. 164:1814-1819, 2000; Spencer, SD et al., J. Exp. Med. 187:571-578, 1998; Gibbs, VC and Pennica Gene 186:97-101, 1997 (CRF2-4 cDNA); Xie, MH et al., J. Biol. Chem. 275: 31335-31339, 2000; and Kotenko, SV et al., J. Biol. Chem. manuscript in press M007837200). Moreover, IL-10.beta. receptor may be involved as a receptor for

IL-TIF, and it is believed to be synonymous with CRF2-4 (Dumoutier, L. et al., Proc. Nat'l. Acad. Sci. 97:10144-10149, 2000; Liu Y et al, J Immunol. 152; 1821-1829, 1994 (IL-10R cDNA). Within preferred embodiments, the soluble receptor form of zcytor16, residues 22-231 of SEQ ID NO:2, (SEQ ID NO:13) is a monomer, homodimer, heterodimer, or multimer that antagonizes the effects of IL-TIF in vivo. Antibodies and binding polypeptides to such zcytor16 monomer, homodimer, heterodimer, or multimers also serve as antagonists of zcytor16 activity.

Summary of Invention Paragraph (306):
[0303] IL-TIF has been shown to be induced in the presence of IL-9, and is suspected to be involved in promoting Th1-type immune responses, and inflammation. IL-9 stimulates proliferation, activation, differentiation and/or induction of immune function in a variety of ways and is implicated in asthma, lung mastocytosis, and other diseases, as well as activates STAT pathways. Antagonists of IL-TIF or IL-9 function can have beneficial use against such human diseases. The present invention provides such novel antagonists of IL-TIF.

Summary of Invention Paragraph (307):
[0304] IL-TIF has been show to be involved in up-regulate the production of acute phase reactants, such as serum amyloid A (SAA), .alpha.1-antichymotrypsin, and haptoglobin, and that IL-TIF expression is increased upon injection of lipopolysaccharide (LPS) in vivo suggesting that IL-TIF is involved in inflammatory response (Dumoutier, L. et al., Proc. Nat'l. Acad. Sci. 97:10144-10149, 2000). Production of acute phase proteins, such as SAA, is considered s short-term survival mechanism where inflammation is beneficial; however, maintenance of acute phase proteins for longer periods contributes to chronic inflammation and can be harmful to human health. For review, see Uhlar, CM and Whitehead, AS, Eur. J. Biochem. 265:501-523, 1999, and Baumann H. and Gauldie, J. Immunology Today 15:74-80, 1994. Moreover, the acute phase protein SAA is implicated in the pathogenesis of several chronic inflammatory diseases, is implicated in atherosclerosis and rheumatoid arthritis, and is the precursor to the amyloid A protein deposited in amyloidosis (Uhlar, CM and Whitehead, supra.). Thus, as IL-TIF acts as a pro-inflammatory molecule and induces production of SAA, antagonists would be useful in treating inflammatory disease and other diseases associated with acute phase response proteins induced by IL-TIF. Such antagonists are provided by the present invention. For example, method of reducing IL-TIF-induced or IL-9 induced inflammation comprises administering to a mammal with inflammation an amount of a composition of soluble zcytor16-comprising receptor sufficient to reduce inflammation. Moreover, a method of suppressing an inflammatory response in a mammal with inflammation can comprise: (1) determining a level of serum amyloid A protein; (2) administering a composition comprising a soluble zcytor16 cytokine receptor polypeptide as described herein in an acceptable pharmaceutical vehicle; (3) determining a post administration level of serum amyloid A protein; (4) comparing the level of serum amyloid A protein in step (1) to the level of serum amyloid A protein in step (3), wherein a lack of increase or a decrease in serum amyloid A protein level is indicative of suppressing an inflammatory response.

Summary of Invention Paragraph (308):
[0305] The receptors of the present invention include at least one zcytor16 receptor subunit. A second receptor polypeptide included in the heterodimeric soluble receptor belongs to the receptor subfamily that includes Interleukin-10 receptor, the interferons (e.g., interferon-gamma alpha and beta chains and the interferon-alpha/beta receptor alpha and beta chains), zcytor7, zcytor1, and CRF2-4. A second soluble receptor polypeptide included in a heterodimeric soluble receptor can also include a zcytor1 soluble receptor subunit, disclosed in the commonly owned U.S. Pat. No. 5,965,704; an L-10R subunit, such as L-10R.alpha.; or a zcytor7 soluble receptor subunit, disclosed in the commonly owned U.S. Pat. No. 5,945,511. The zcytor11 receptor in conjunction with CRF2-4 and IL-10 Receptor was shown to signal JAK-STAT pathway in response to IL-TIF (Xie et al., supra.; Kotenko et al., supra.). According to the present invention, in addition to a monomeric or homodimeric zcytor16 receptor polypeptide, a heterodimeric soluble zcytor16 receptor, as exemplified by an embodiment comprising a soluble zcytor16 receptor+soluble CRF2-4 receptor heterodimer (zcytor16/CRF2-4), can act as an antagonist of the IL-TIF. Other embodiments include soluble heterodimers comprising zcytor16/IL-10R, zcytor16/IL-9R, zcytor16/zcytor1, zcytor16/zcytor7, and other class II receptor subunits, as well as multimeric receptors including but not limited to zcytor16/CRF2-4/zcytor1 or

zcytor16/CRF2-4/IL-10R.

Summary of Invention Paragraph (309):
[0306] Analysis of the tissue distribution of the mRNA corresponding zcytor16 cDNA showed that mRNA level was highest in placenta and spleen, and the ligand to which zcytor16 binds (IL-TIF) is implicated in inducing inflammatory response including induction of the acute-phase response (Dumoutier, L. et al., Proc. Nat'l. Acad. Sci. 97:10144-10149, 2000). Thus, particular embodiments of the present invention are directed toward use of soluble zcytor16 heterodimers as antagonists in inflammatory and immune diseases or conditions such as pancreatitis, type I diabetes (IDDM), pancreatic cancer, pancreatitis, Graves Disease, inflammatory bowel disease (IBD), Crohn's Disease, colon and intestinal cancer, diverticulosis, autoimmune disease, sepsis, organ or bone marrow transplant; inflammation due to trauma, sugery or infection; amyloidosis; splenomegaly; graft versus host disease; and where inhibition of inflammation, immune suppression, reduction of proliferation of hematopoietic, immune, inflammatory or lymphoid cells, macrophages, T-cells (including Th1 and Th2 cells), suppression of immune response to a pathogen or antigen, or other instances where inhibition of IL-TIF or IL-9 cytokine production is desired.

Summary of Invention Paragraph (311):
[0308] 1) Antagonize or block signaling via the IL-TIF receptors in the treatment of acute inflammation, inflammation as a result of trauma, tissue injury, surgery, sepsis or infection, and chronic inflammatory diseases such as asthma, inflammatory bowel disease (IBD), chronic colitis, splenomegaly, rheumatoid arthritis, recurrent acute inflammatory episodes (e.g., tuberculosis), and treatment of amyloidosis, and atherosclerosis, Castleman's Disease, asthma, and other diseases associated with the induction of acute-phase response.

Summary of Invention Paragraph (312):
[0309] 2) Antagonize or block signaling via the IL-TIF receptors in the treatment of autoimmune diseases such as IDDM, multiple sclerosis (MS), systemic Lupus erythematosus (SLE), myasthenia gravis, rheumatoid arthritis, and IBD to prevent or inhibit signaling in immune cells (e.g. lymphocytes, monocytes, leukocytes) via zcytor16 (Hughes C et al., J. Immunol 153: 3319-3325, 1994). Alternatively antibodies, such as monoclonal antibodies (MAb) to zcytor16-comprising receptors, can also be used as an antagonist to deplete unwanted immune cells to treat autoimmune disease. Asthma, allergy and other atopic disease may be treated with an MAb against, for example, soluble zcytor16 soluble receptors or zcytor16/CRF2-4 heterodimers, to inhibit the immune response or to deplete offending cells. Blocking or inhibiting signaling via zcytor16, using the polypeptides and antibodies of the present invention, may also benefit diseases of the pancreas, kidney, pituitary and neuronal cells. IDDM, NIDDM, pancreatitis, and pancreatic carcinoma may benefit. Zcytor16 may serve as a target for MAb therapy of cancer where an antagonizing MAb inhibits cancer growth and targets immune-mediated killing. (Holliger P, and Hoogenboom, H: Nature Biotech. 16: 1015-1016, 1998). Mabs to soluble zcytor16 monomers, homodimers, heterodimers and multimers may also be useful to treat nephropathies such as glomerulosclerosis, membranous neuropathy, amyloidosis (which also affects the kidney among other tissues), renal arteriosclerosis, glomerulonephritis of various origins, fibroproliferative diseases of the kidney, as well as kidney dysfunction associated with SLE, IDDM, type II diabetes (NIDDM), renal tumors and other diseases.

Summary of Invention Paragraph (313):
[0310] 3) Agonize or initiate signaling via the IL-TIF receptors in the treatment of autoimmune diseases such as IDDM, MS, SLE, myasthenia gravis, rheumatoid arthritis, and IBD. Anti-soluble zcytor16, anti-soluble zcytor16/CRF2-4 heterodimers and multimer monoclonal antibodies may signal lymphocytes or other immune cells to differentiate, alter proliferation, or change production of cytokines or cell surface proteins that ameliorate autoimmunity. Specifically, modulation of a T-helper cell response to an alternate pattern of cytokine secretion may deviate an autoimmune response to ameliorate disease (Smith J A et al., J. Immunol. 160:4841-4849, 1998). Similarly, agonistic Anti-soluble zcytor16, anti-solublezcytor16/CRF2-4 heterodimers and multimer monoclonal antibodies may be used to signal, deplete and deviate immune cells involved in asthma, allergy and atopoic disease. Signaling via zcytor16 may also benefit diseases of the pancreas, kidney, pituitary and neuronal cells. IDDM, NIDDM, pancreatitis, and pancreatic carcinoma may benefit. Zcytor16 may serve as a target for

MAb therapy of pancreatic cancer where a signaling MAb inhibits cancer growth and targets immune-mediated killing (Tutt, A L et al., J Immunol. 161: 3175-3185, 1998). Similarly renal cell carcinoma may be treated with monoclonal antibodies to zcytor16-comprising soluble receptors of the present invention.

Summary of Invention Paragraph (314):
[0311] Soluble zcytor16 monomeric, homodimeric, heterodimeric and multimeric polypeptides described herein can be used to neutralize/block IL-TIF activity in the treatment of autoimmune disease, atopic disease, NIDDM, pancreatitis and kidney dysfunction as described above. A soluble form of zcytor16 may be used to promote an antibody response mediated by Th cells and/or to promote the production of IL-4 or other cytokines by lymphocytes or other immune cells.

Summary of Invention Paragraph (315):
[0312] The soluble zcytor16-comprising receptors of the present invention are useful as antagonists of the IL-TIF cytokine. Such antagonistic effects can be achieved by direct neutralization or binding of the IL-TIF. In addition to antagonistic uses, the soluble receptors of the present invention can bind IL-TIF and act as carrier proteins for the IL-TIF cytokine, in order to transport the Ligand to different tissues, organs, and cells within the body. As such, the soluble receptors of the present invention can be fused or coupled to molecules, polypeptides or chemical moieties that direct the soluble-receptor-Ligand complex to a specific site, such as a tissue, specific immune cell, or tumor. For example, in acute infection or some cancers, benefit may result from induction of inflammation and local acute phase response proteins by the action of IL-TIF. Thus, the soluble receptors of the present invention can be used to specifically direct the action of the IL-TIF. See, Cosman, D. Cytokine 5: 95-106, 1993; and Fernandez-Botran, R. Exp. Opin. Invest. Drugs 9:497-513, 2000.

Summary of Invention Paragraph (316):
[0313] Moreover, the soluble receptors of the present invention can be used to stabilize the IL-TIF, to increase the bioavailability, therapeutic longevity, and/or efficacy of the Ligand by stabilizing the Ligand from degradation or clearance, or by targeting the ligand to a site of action within the body. For example the naturally occurring IL-6/soluble IL-6R complex stabilizes IL-6 and can signal through the gp130 receptor. See, Cosman, D. supra., and Fernandez-Botran, R. supra.. Moreover, Zcytor16 may be combined with a cognate ligand such as IL-TIF to comprise a ligand/soluble receptor complex. Such complexes may be used to stimulate responses from cells presenting a companion receptor subunit such as, for example, zcytor11 or CRF2-4. The cell specificity of zcytor16/ligand complexes may differ from that seen for the ligand administered alone. Furthermore the complexes may have distinct pharmacokinetic properties such as affecting half-life, dose/response and organ or tissue specificity. ZcytoR16/IL-TIF complexes thus may have agonist activity to enhance an immune response or stimulate mesangial cells or to stimulate hepatic cells. Alternatively only tissues expressing a signaling subunit the heterodimerizes with the complex may be affected analogous to the response to IL6/IL6R complexes (Hirota H. et al., Proc. Nat'l. Acad. Sci. 92:4862-4866, 1995; Hirano, T. in Thomason, A. (Ed.) "The Cytokine Handbook", 3.sup.rd Ed., p. 208-209). Soluble receptor/cytokine complexes for IL12 and CNTF display similar activities.

Summary of Invention Paragraph (317):
[0314] Zcytor16 homodimeric, heterodimeric and multimeric receptor polypeptides may also be used within diagnostic systems for the detection of circulating levels of IL-TIF ligand, and in the detection of IL-TIF associated with acute phase inflammatory response. Within a related embodiment, antibodies or other agents that specifically bind to Zcytor16 soluble receptors of the present invention can be used to detect circulating receptor polypeptides; conversely, Zcytor16 soluble receptors themselves can be used to detect circulating or locally-acting IL-TIF polypeptides. Elevated or depressed levels of ligand or receptor polypeptides may be indicative of pathological conditions, including inflammation or cancer. IL-TIF is known to induce associated acute phase inflammatory response. Moreover, detection of acute phase proteins or molecules such as IL-TIF can be indicative of a chronic inflammatory condition in certain disease states (e.g., rheumatoid arthritis). Detection of such conditions serves to aid in disease diagnosis as well as help a physician in choosing proper therapy.

Summary of Invention Paragraph (318):
[0315] Moreover, soluble zcytor16 receptor polypeptides of the present invention can be used as a "ligand sink," i.e., antagonist, to bind ligand in vivo or in vitro in therapeutic or other applications where the presence of the ligand is not desired. For example, in chronic inflammatory conditions or cancers that are expressing large amounts of bioactive IL-TIF, soluble zcytor16 receptor or soluble zcytor16 heterodimeric and multimeric receptor polypeptides, such as soluble zcytor16/CRF2-4 can be used as a direct antagonist of the ligand in vivo, and may aid in reducing progression and symptoms associated with the disease, and can be used in conjunction with other therapies (e.g., steroid or chemotherapy) to enhance the effect of the therapy in reducing progression and symptoms, and preventing relapse. Moreover, soluble zcytor16 receptor polypeptides can be used to slow the progression of cancers that over-express zcytor16 receptors, by binding ligand in vivo that could otherwise enhance proliferation of those cancers.

Summary of Invention Paragraph (319):
[0316] Moreover, soluble zcytor16 receptor polypeptides of the present invention can be used in vivo or in diagnostic applications to detect IL-TIF-expressing inflammation or cancers in vivo or in tissue samples. For example, the soluble zcytor16 receptors of the present invention can be conjugated to a radio-label or fluorescent label as described herein, and used to detect the presence of the IL-TIF in a tissue sample using an in vitro ligand-receptor type binding assay, or fluorescent imaging assay. Moreover, radiolabeled soluble zcytor16 receptors of the present invention could be administered in vivo to detect Ligand-expressing solid tumors through a radio-imaging method known in the art.

Summary of Invention Paragraph (384):
[0381] Within another aspect the present invention provides an isolated polynucleotide that encodes a soluble cytokine receptor polypeptide comprising a sequence of amino acid residues that is at least 90% identical to the amino acid sequence as shown in SEQ ID NO:2 from amino acid 22-231 or 22-210, and wherein the soluble cytokine receptor polypeptide encoded by the polynucleotide sequence binds IL-TIF or antagonizes IL-TIF activity.

Summary of Invention Paragraph (390):
[0387] Within another aspect the present invention provides a cultured cell into which has been introduced an expression vector as disclosed above, wherein the cell expresses a heterodimeric or multimeric soluble receptor polypeptide encoded by the DNA segments. In one embodiment is provided a cell as disclosed above, wherein the cell secretes a soluble cytokine receptor polypeptide heterodimer or multimeric complex. In another embodiment is provided a cell as disclosed above, wherein the cell secretes a soluble cytokine receptor polypeptide heterodimer or multimeric complex that binds IL-TIF or antagonizes IL-TIF activity.

Summary of Invention Paragraph (395):
[0392] Within another aspect the present invention provides an isolated soluble cytokine receptor polypeptide comprising a sequence of amino acid residues that is at least 90% identical to an amino acid sequence as shown in SEQ ID NO:2 from amino acid 22-231 or 22-210, and wherein the soluble cytokine receptor polypeptide binds IL-TIF or antagonizes IL-TIF activity.

Detail Description Paragraph (40):
[0433] Soluble zcytor16 receptor (Example 11), or gp130 (Hibi, M. et al., Cell 63:1149-1157, 1990) are biotinylated by reaction with a five-fold molar excess of sulfo-NHS-LC-Biotin (Pierce, Inc., Rockford, Ill.) according to the manufacturer's protocol. Soluble zcytor16 receptor and another soluble receptor subunit, for example, soluble IL-10R (sIL-10R) or CRF2-4 receptor (CRF2-4), soluble zcytor11 receptor (US Pat. No. 5,965,704) or soluble zcytor7 receptor (U.S. Pat. No. 5,945,511) are labeled with a five fold molar excess of Ru-BPY-NHS (Igen, Inc., Gaithersburg, Md.) according to manufacturer's protocol. The biotinylated and Ru-BPY-NHS-labeled forms of the soluble zcytor16 receptor can be respectively designated Bio-zcytor16 receptor and Ru-zcytor16; the biotinylated and Ru-BPY-NHS-labeled forms of the other soluble receptor subunit can be similarly designated. Assays can be carried out using conditioned media from cells expressing a ligand, such as IL-TIF, that binds zcytor16 heterodimeric receptors, or using purified IL-TIF.

Detail Description Paragraph (56):
[0445] Using standard methods described herein, cells expressing a BaF3/zcytor16-MPL chimera (wherein the extracellular domain of the zcytor16 (e.g., SEQ ID NO:13) is fused in frame to the intracellular signaling domain of the mpl receptor) are tested for proliferative response in the presence of IL-TIF. Such cells serve as a bioassay cell line to measure ligand binding of monomeric or homodimeric zcytor16 receptors. In addition, BaF3/zcytor16-MPL chimera cells transfected with an additional heterodimeric cytokine receptor subunit can be assessed for proliferative response in the presence of IL-TIF. In the presence of IL-TIF, if the BaF3/zcytor16-MPL cells signal, this would suggest that zcytor16 receptor can homodimerize to signal. Transfection of the BaF3/MPL-zcytor16 cell line with and additional MPL-class II cytokine receptor fusion that signals in the presence of the IL-TIF ligand, such as CRF2-4, determines which heterodimeric cytokine receptor subunits are required for zcytor16 receptor signaling. Use of MPL-receptor fusions for this purpose alleviates the requirement for the presence of an intracellular signaling domain for the zcytor16 receptor.

Detail Description Paragraph (57):
[0446] Each independent receptor complex cell line is then assayed in the presence of IL-TIF and proliferation measured using routine methods (e.g., Alamar Blue assay). The BaF3/MPL-zcytor16 bioassay cell line serves as a control for the monomeric or homodimeric receptor activity, and is thus used as a baseline to compare signaling by the various receptor complex combinations. The untransfected bioassay cell line serves as a control for the background activity, and is thus used as a baseline to compare signaling by the various receptor complex combinations. A BaF3/MPL-zcytor16 without ligand (IL-TIF) is also used as a control. The IL-TIF in the presence of the correct receptor complex, is expected to increase proliferation of the BaF3/zcytor16-MPL receptor cell line approximately 5 fold over background or greater in the presence of IL-TIF. Cells expressing the components of zcytor16 heterodimeric and multimeric receptors should proliferate in the presence of IL-TIF.

Detail Description Paragraph (60):
[0447] To identify components involved in the zcytor16-signaling complex, receptor reconstitution studies are performed as follows. BHK 570 cells (ATCC No. CRL-10314) transfected, using standard methods described herein, with a luciferase reporter mammalian expression vector plasmid serve as a bioassay cell line to measure signal transduction response from a transfected zcytor16 receptor complex to the luciferase reporter in the presence of IL-TIF. BHK cells do not endogenously express the zcytor16 receptor. An exemplary luciferase reporter mammalian expression vector is the KZ134 plasmid which was constructed with complementary oligonucleotides that contain STAT transcription factor binding elements from 4 genes. A modified c-fos Sis inducible element (m67SIE, or hSIE) (Sadowski, H. et al., Science 261:1739-1744, 1993), the p21 SIE1 from the p21 WAF1 gene (Chin, Y. et al., Science 272:719-722, 1996), the mammary gland response element of the .beta.-casein gene (Schmitt-Ney, M. et al., Mol. Cell. Biol. 11:3745-3755, 1991), and a STAT inducible element of the Fcg RI gene, (Seidel, H. et al., Proc. Natl. Acad. Sci. 92:3041-3045, 1995). These oligonucleotides contain Asp718-XhoI compatible ends and were ligated, using standard methods, into a recipient firefly luciferase reporter vector with a c-fos promoter (Poulsen, L. K. et al., J. Biol. Chem. 273:6229-6232, 1998) digested with the same enzymes and containing a neomycin selectable marker. The KZ134 plasmid is used to stably transfect BHK, or BaF3 cells, using standard transfection and selection methods, to make a BHK/KZ134 or BaF3/KZ134 cell line respectively.

Detail Description Paragraph (67):
[0452] Since zcytor16 is a Class II cytokine receptor, the binding of zcytor16sR/Fc4 fusion protein with known or orphan Class II cytokines was tested. The pZP7 expression vectors containing cDNAs of cytokines (including human IL-TIF, interferon alpha, interferon beta, interferon gamma, IL-10, amongst others) were transfected into COS cells, and the binding of zcytor16sR/Fc4 to transfected COS cells were carried out using the secretion trap assay described above. Human IL-TIF showed positive binding. Based on these data, human IL-TIF and zcytor16 is a potential ligand-receptor pair.

Detail Description Paragraph (82):
[0463] In addition, because the expression pattern of zcytor16, one of IL-TIF's receptors, shows expression in certain specific tissues as well as tissue-specific

tumors, binding partners including the natural liganed, IL-TIF, can also be used as a diagnostic to detect specific tissues (normal or abnormal), cancer, or cancer tissue in a biopsy, tissue, or histologic sample, where IL-TIF receptors are expressed, and particularly e.g., ovarian cancer, stomach cancer, uterine cancer, rectal cancer, lung cancer and esophageal cancer tissue. IL-TIF can also be used to target other tissues wherein its receptors, e.g., zcytor16 and zcytor11 are expressed. Moreover, such binding partners could be conjugated to chemotherapeutic agents, toxic moieties and the like to target therapy to the site of a tumor or diseased tissue. Such diagnostic and targeted therapy uses are known in the art and described herein.

Detail Description Paragraph (96):
[0473] BaF3 cells expressing the full-length CFR2-4 receptor were constructed, using 30 .mu.g of a CFR2-4 expression vector, described below. The BaF3 cells expressing the CFR2-4 receptor were designated as BaF3/CFR2-4. These cells were used as a control, and were further transfected with full-length zcytor11 receptor (U.S. Pat. No. 5,965,704) and used to construct a screen for IL-TIF activity as described below.

Detail Description Paragraph (101):
[0478] BaF3/CRF2-4 cells expressing the full-length zcytor11 receptor were constructed as per Example 5A above, using 30 .mu.g of the zcytor11 expression vector, described in Example 6 above. Following recovery, transfectants were selected using 200 .mu.g/ml zeocin and 2 .mu.g/ml puromycin. The BaF3/CRF2-4 cells expressing the zcytor11 receptor were designated as BaF3/CRF2-4/zcytor11 cells. These cells were used to screen for IL-TIF activity as well as zcytor16 antagonist activity described IN Example 15.

Detail Description Paragraph (103):
Screening for IL-TIF antagonist activity using BaF3/CRF2-4/zcytor11 cells using an Alamar Blue Proliferation Assay

Detail Description Paragraph (104):
[0479] A. Screening for IL-TIF activity using BaF3/CRF2-4/zcvtorl 1 cells using an Alamar Blue Proliferation Assay

Detail Description Paragraph (105):
[0480] Purified IL-TIF-CEE (Example 19) was used to test for the presence of proliferation activity as described below. Purified zcytor16-Fc4 (Example 11) was used to antagonize the proliferative response of the IL-TIF in this assay as described below.

Detail Description Paragraph (107):
[0482] Proliferation of the BaF3/CRF2-4/zcytor11 cells was assessed using IL-TIF-CEE protein diluted with mIL-3 free media to 50, 10, 2, 1, 0.5, 0.25, 0.13, 0.06 ng/ml concentrations. 100 .mu.l of the diluted protein was added to the BaF3/CRF2-4/zcytor11 cells. The total assay volume is 200 .mu.l. The assay plates were incubated at 37.degree. C., 5% CO.sub.2 for 3 days at which time Alamar Blue (Accumed, Chicago, Ill.) was added at 20 .mu.l/well. Plates were again incubated at 37.degree. C., 5% CO.sub.2 for 24 hours. Alamar Blue gives a fluourometric readout based on number of live cells, and is thus a direct measurement of cell proliferation in comparison to a negative control. Plates were again incubated at 37.degree. C., 5% CO.sub.2 for 24 hours. Plates were read on the Fmax.TM. plate reader (Molecular Devices Sunnyvale, Calif.) using the SoftMax.TM. Pro program, at wavelengths 544 (Excitation) and 590 (Emmission). Results confirmed the dose-dependent proliferative response of the BaF3/CRF2-4/zcytor11 cells to a IL-TIF-CEE. The response, as measured, was approximately 15-fold over background at the high end of 50 ng/ml down to a 2-fold induction at the low end of 0.06 ng/ml. The BaF3 wild type cells, and BaF3/CRF2-4 cells did not proliferate in response to IL-TIF-CEE, showing that IL-TIF is specific for the CRF2-4/zcytor11 heterodimeric receptor.

Detail Description Paragraph (108):
[0483] In order to determine if zcytor16 is capable of antagonizing IL-TIF activity, the assay described above was repeated using purified soluble zcytor16/Fc4. When IL-TIF was combined with zcytor16 at 10 .mu.g/ml, the response to IL-TIF at all concentrations was brought down to background. That the presence of soluble zcytor16 ablated the proliferative effects of IL-TIF demonstrates that it is a potent

antagonist of the IL-TIF ligand.

Detail Description Paragraph (110):
IL-TIF Activation of a Reporter Mini-gene in MES 13 Cells and Inhibition of Activity by zcytor16-Fc4

Detail Description Paragraph (111):
[0484] MES 13 cells (ATCC No. CRL-1927) were plated at 10,000 cells/well in 96-well tissue culture clusters (Costar) in DMEM growth medium (Life Technologies) supplemented with pyruvate and 10% serum (HyClone). Next day, the medium was switched to serum free DMEM medium by substituting 0.1% BSA (Fraction V; Sigma) for serum. This medium also contained the adenoviral construct KZ136 (below) that encodes a luciferase reporter mini-gene driven by SRE and STAT elements, at a 1000:1 multiplicity of infection (m.o.i.), i.e. 1000 adenoviral particles per cell. After allowing 24 h for the incorporation of the adenoviral construct in the cells, the media were changed and replaced with serum-free media. Human recombinant IL-TIF with or without a recombinant zcytor16-Fc4 fusion was added at the indicated final concentration in the well (as described in Table 11, below). Dilutions of both the IL-TIF and zcytor16-Fc4 were performed in serum-free medium. 0.1% BSA was added for a basal assay control. 4 h later, cells were lysed and luciferase activity, denoting activation of the reporter gene, was determined in the lysate using an Luciferase Assay System assay kit (Promega) and a Labsystems Luminoskan luminometer (Labsystems, Helsinki, Finland). Activity was expressed as luciferase units (LU) in the lysate. Results are shown in Table 11, below.

Detail Description Paragraph (112):
[0485] These results demonstrate two things: First, that MES 13 cells respond to human recombinant IL-TIF and therefore possess endogenous functional receptors for the cytokine. Second, that the zcytoR16-Fc4 receptor fusion acts as an antagonist that effectively blocks the response to IL-TIF, even at the highest dose that this cytokine was used. Therefore, zcyto16 is an effective antagonist of IL-TIF on cells (MES 13) that are intrinsically capable of responding to IL-TIF, i.e. cells that do not require exogenous expression of additional receptor components to respond to the cytokine.

Detail Description Paragraph (115):
Construct for Generating CEE-tagged IL-TIF

Detail Description Paragraph (116):
[0487] Oligonucleotides were designed to generate a PCR fragment containing the Kozak sequence and the coding region for IL-TIF, without its stop codon. These oligonucleotides were designed with a KpnI site at the 5' end and a BamHI site at the 3' end to facilitate cloning into pHZ200-CEE, our standard vector for mammalian expression of C-terminal Glu-Glu tagged (SEQ ID NO:10) proteins. The pHZ200 vector contains an MT-1 promoter.

Detail Description Paragraph (117):
[0488] PCR reactions were carried out using Turbo Pfu polymerase (Stratagene) to amplify a IL-TIF cDNA fragment. About 20 ng human IL-TIF polynucleotide template (SEQ ID NO: 14), and oligonucleotides ZC28590 (SEQ ID NO:28) and ZC28580 (SEQ ID NO:29) were used in the PCR reaction. PCR reaction conditions were as follows: 95.degree. C. for 5 minutes,; 30 cycles of 95.degree. C. for 60 seconds, 55.degree. C. for 60 seconds, and 72.degree. C. for 60 seconds; and 72.degree. C. for 10 minutes; followed by a 4.degree. C. hold. PCR products were separated by agarose gel electrophoresis and purified using a QiaQuick.TM. (Qiagen) gel extraction kit. The isolated, approximately 600 bp, DNA fragment was digested with KpnI and BamHI (Boerhinger-Mannheim), gel purified as above and ligated into pHZ200-CEE that was previously digested with KpnI and BamHI.

Detail Description Paragraph (118):
[0489] About one microliter of the ligation reaction was electroporated into DH10B ElectroMax.TM. competent cells (GIBCO BRL, Gaithersburg, Md.) according to manufacturer's direction and plated onto LB plates containing 100 .mu.g/ml ampicillin, and incubated overnight. Colonies were picked and screened by PCR using oligonucleotides ZC28,590 (SEQ ID NO:28) and ZC28,580 (SEQ ID NO:29), with PCR conditions as described above. Clones containing inserts were then sequenced to

confirm error-free IL-TIF inserts. Maxipreps of the correct pHZ200-IL-TIF-CEE construct, as verified by sequence analysis, were performed.

Detail Description Paragraph (120):
Transfection And Expression Of IL-TIF Soluble Receptor Polypeptides

Detail Description Paragraph (125):
Purification of IL-TIF Soluble Receptors from BHK 570 cells

Detail Description Paragraph (126):
[0493] Unless otherwise noted, all operations were carried out at 4.degree. C. The following procedure was used for purifying IL-TIF polypeptide containing C-terminal GluGlu (EE) tags (SEQ ID NO:10). Conditioned media from BHK cells expressing IL-TIF-CEE (Example 18) was concentrated with an Amicon S10Y3 spiral cartridge on a ProFlux A30. A Protease inhibitor solution was added to the concentrated conditioned media to final concentrations of 2.5 mM ethylenediaminetetraacetic acid (EDTA, Sigma Chemical Co. St. Louis, Mo.), 0.003 mM leupeptin (Boehringer-Mannheim, Indianapolis, Ind.), 0.001 mM pepstatin (Boehringer-Mannheim) and 0.4 mM Pefabloc (Boehringer-Mannheim). Samples were removed for analysis and the bulk volume was frozen at -80.degree. C. until the purification was started. Total target protein concentrations of the concentrated conditioned media were determined via SDS-PAGE and Western blot analysis with the anti-EE HRP conjugated antibody.

Detail Description Paragraph (140):
[0505] In addition, because the expression pattern of zcytor11, one of IL-TIF's receptors, shows expression in certain specific tissues, binding partners including the natural ligand, IL-TIF, can also be used as a diagnostic to detect specific tissues (normal or abnormal), cancer, or cancer tissue in a biopsy, tissue, or histologic sample, particularly in tissues where IL-TIF receptors are expressed. IL-TIF can also be used to target other tissues wherein its receptors, e.g., zcytor16 and zcytor11 are expressed. Moreover, such binding partners could be conjugated to chemotherapeutic agents, toxic moieties and the like to target therapy to the site of a tumor or diseased tissue. Such diagnostic and targeted therapy uses are known in the art and described herein.

Detail Description Paragraph (141):
[0506] The expression patterns of zcytor11 (above) and zcytor16 (Example 12, and Example 21) indicated target tissues and cell types for the action of IL-TIF, and hence IL-TIF antagonsists, such as zcytor16. The zcytor11 expression generally overlapped with zcytor16 expression in three physiologic systems: digestive system, female reproductive system, and immune system. Moreover, the expression pattern of the receptor (zcytor11) indicated that an IL-TIF antagonist such as zcytor16 would have therapeutic application for human disease in two areas: inflammation (e.g., IBD, Chron's disease, pancreatitis) and cancer (e.g., ovary, colon). That is, the polynucleotides, polypeptides and antibodies of the present invention can be used to antagonize the inflammatory, and other cytokine-induced effects of IL-TIF interaction with the cells expressing the zcytor11 receptor.

Detail Description Paragraph (142):
[0507] Moreover, the expression of zcytor11 appeared to be downregulated or absent in an ulcerative colitis tissue, HepG2 liver cell line induced by IL-6, activated CD8+ T-cells and CD19+ B-cells. However, zcytor16 appeared to be upregulated in activated CD19+ B-cells (Example 12), while zcytor11 is downregulated in activated CD19+ cells, as compared to the resting CD19+ cells (above). The expression of zcytor11 and zcytor16 has a reciprocal correlation in this case. These RT-PCR experiments demonstrate that CD19+ peripheral blood cells, B lymphocytes, express receptors for IL-TIF, namely zcytoR11 and zcytoR16. Furthermore B cells display regulated expression of zcytoR11 and zcytoR16. B-lymphocytes activated with mitogens decrease expression of zcytoR11 and increase expression of zcytoR16. This represents a classical feedback inhibition that would serve to dampen the activity of IL-TIF on B cells and other cells as well. Soluble zcytoR16 would act as an antagonist to neutralize the effects of IL-TIF on B cells. This would be beneficial in diseases where B cells are the key players: Autoimmune diseases including systemic lupus erythmatosus (SLE), myasthenia gravis, immune complex disease, and B-cell cancers that are exacerbated by IL-TIF. Also autoimmune diseases where B cells contribute to the disease pathology would be

targets for zcytoR16 therapy: Multiple sclerosis, inflammatory bowel disease (IBD) and rheumatoid arthritis are examples. ZcytoR16 therapy would be beneficial to dampen or inhibit B cells producing IgE in atopic diseases including asthma, allergy and atopic dermatitis where the production of IgE contributes to the pathogenesis of disease.

Detail Description Paragraph (143):
[0508] B cell malignancies may exhibit a loss of the "feedback inhibition" described above. Administration of zcytoR16 would restore control of IL-TIF signaling and inhibit B cell tumor growth. The administration of zcytoR16 following surgical resection or chemotherapy may be useful to treat minimal residual disease in patients with B cell malignancies. The loss of regulation may lead to sustain or increased expression of zcytoR11. Thus creating a target for therapeutic monoclonal antibodies targeting zcytoR11.

Detail Description Paragraph (150):
[0513] In summary, the in situ data was consistent, with expression data described above for the zcytor16. Zcytor16 expression was observed predominately in mononuclear cells, and a subset of epithelium was also positive. These results confirmed the presence of zcytor16 expression in immune cells and point toward a role in inflammation, autoimmune disease, or other immune function, for example, in binding pro-inflammatory cytokines, including but not limited to IL-TIF. Moreover, detection of zcytor16 expression can be used for example as an marker for mononuclear cells in histologic samples.

Detail Description Paragraph (151):
[0514] Zcytor16 is expressed in mononuclear cells, including normal tissues (lymph nodes, spleen, thymus, pancreas and fetal liver, lung), and abnormal tissues (inflamed appendix, lung carcinoma, ovary carcinoma, pancreatitis, inflamed skin, and prostate carcinoma). It is notable that plasma cells in the lymph node, intestine, and lung carcinoma are positive for zcytor16. Plasma cells are immunologically activated lymphocytes responsible for antibody synthesis. In addition, IL-TIF, is expressed in activated T cells. In addition, the expression of zcytor16 is detected only in activated (but not in resting) CD4+ and CD19+ cells (Example 12). Thus, zcytor16 can be used as a marker for or as a target in isolating certain lymphocytes, such as mononuclear leucocytes and limited type of activated leucocytes, such as activated CD4+ and CD19+.

Detail Description Paragraph (156):
In vivo Affects of IL-TIF Polypeptide

Detail Description Paragraph (157):
[0518] Mice (female, C57B1, 8 weeks old; Charles River Labs, Kingston, N.Y.) were divided into three groups. An adenovirus expressing an IL-TIF polypeptide (# SEQ ID NO:15) was previously made using standard methods. On day 0, parental or IL-TIF adenovirus was administered to the first (n=8) and second (n=8) groups, respectively, via the tail vein, with each mouse receiving a dose of .about.1.times.10.sup.11 particles in .about.0.1 ml volume. The third group (n=8) received no treatment. On days 12, mice were weighed and blood was drawn from the mice. Samples were analyzed for complete blood count (CBC) and serum chemistry. Statistically significant elevations in neutrophil and platelet counts were detected in the blood samples from the IL-TIF adenovirus administered group relative to the parental adenovirus treated group. Also, lymphocyte and red blood cell counts were significantly reduced from the IL-TIF adenovirus administered group relative to the parental adenovirus treated group. In addition, the IL-TIF adenovirus treated mice decreased in body weight, while parental adenovirus treated mice gained weight.

Detail Description Paragraph (158):
[0519] The results suggested that IL-TIF affects hematopoiesis, i.e., blood cell formation in vivo. As such, IL-TIF could have biological activities effecting different blood stem cells, thus resulting increase or decrease of certain differentiated blood cells in a specific lineage. For instance, IL-TIF appears to reduce lymphocytes, which is likely due to inhibition of the committed progenitor cells that give rise to lymphoid cells. IL-TIF also decreases red blood cells. This finding agrees with the inhibitory effects of IL-TIF on the proliferation and/or growth of myeloid stem cells (Example 23), supporting the notion that IL-TIF could

play a role in anemia, infection, inflammation, and/or immune diseases by influencing blood cells involved in these process. Antagnists against IL-TIF, such as antibodies or its soluble receptor zcytor16, could be used as therapeutic reagents in these diseases.

Detail Description Paragraph (159):
[0520] Moreover, these experiments using IL-TIF adenovirus in mice suggest that IL-TIF over-expression increases the level of neutrophils and platelets in vivo. Although this may appear contradictory to the finding seen in K562 cells (Example 23), it is not uncommon to observe diverse activities of a particular protein in vitro versus in vivo. It is conceivable that there are other factors (such as cytokines and modifier genes) involved in the responses to IL-TIF in the whole animal system. Nevertheless, these data strongly support the involvement of IL-TIF in hematopoiesis. Thus, IL-TIF and its receptors are suitable reagents/targets for the diagnosis and treatment in variety of disorders, such as inflammation, immune disorders, infection, anemia, hematopoietic and other cancers, and the like.

Detail Description Paragraph (161):
The IL-TIF Polypeptide Lyses K-562 Cells in Cytotoxicity Assay

Detail Description Paragraph (163):
[0522] K562 cells were plated at 5,000 cells/well in 96-well tissue culture clusters (Costar) in DMEM phenol-free growth medium (Life Technologies) supplemented with pyruvate and 10% serum (HyClone). Next day, human recombinant IL-TIF (Example 19), BSA control or retinoic acid (known to be cytotoxic to K562 cells) were added. Seventy-two hours later, the vital stain MTT (Sigma, St Louis, Mo.), a widely used indicator of mitochondrial activity and cell growth, was added to the cells at a final concentration of 0.5 mg/ml. MMP is converted to a purple formazan derivative by mitochondrial dehydrogenases. Four hours later, converted MMP was solubilized by adding an equal volume of acidic isopropanol (0.04 N HC1 in absolute isopropanol) to the wells. Absorbance was measured at 570 nm, with background subtraction at 650 nm. In this experimental setting, absorbance reflects cell viability. Results shown in Table 12 are expressed as % cytotoxicity.

Detail Description Paragraph (164):
[0523] The results indicate that IL-TIF may affect myeloid stem cells. Myeloid stem cells are daughter cells of the universal blood stem cells. They are progenitors of erythrocytes, platelets megakaryocytes, monocytes (or migrated macrophages), neutrophil and basophil, etc. Since K-562 blasts spontaneously differentiate into progenitors of the erythrocytic, granulocytic and monocytic series, it can be considered as myeloid stem cells. Thus, the results demonstrate that IL-TIF has an inhibitory activity on the proliferation and/or growth of myeloid stem cells. Thus IL-TIF could play a role in anemia, infection, inflammation, and/or immune diseases. In addition, an antaganist against IL-TIF, such as antibodies or its soluble receptor zcytor16, could be used to block IL-TIF's activity on myeloid stem cells, or as therapeutic reagents in diseases such as anemia, infection, inflammation, and/or immune diseases.

Detail Description Table CWU (7):
11TABLE 11 Level of IL-TIF (ng/ml) LU w/o zcytoR16 LU w/10 .mu.g/ml zcytoR16 0 (basal BSA control) 103 .+-. 2 104 .+-. 2 0.03 105 .+-. 3 104 .+-. 4 0.3 108 .+-. 4 99 .+-. 6 3 134 .+-. 8 98 .+-. 15 30 188 .+-. 16 110 .+-. 3 300 258 .+-. 21 112 .+-. 30

Detail Description Table CWU (8):
12 TABLE 12 Agent Concentration % Cytotoxicity BSA Control 1 ug/ml 1.3 Retinoic acid 100 uM 62 IL-TIF 100 ng/ml 16.2 IL-TIF 300 ng/ml 32

CLAIMS:

21. An isolated polynucleotide that encodes a soluble cytokine receptor polypeptide comprising a sequence of amino acid residues that is at least 90% identical to the amino acid sequence as shown in SEQ ID NO:2 from amino acid 22-231 or 22-210, and wherein the soluble cytokine receptor polypeptide encoded by the polynucleotide sequence binds IL-TIF or antagonizes IL-TIF activity.

37. A cell according to claim 33, wherein the cell secretes a soluble cytokine receptor polypeptide heterodimer or multimeric complex that binds IL-TIF or antagonizes IL-TIF activity.

43. An isolated soluble cytokine receptor polypeptide comprising a sequence of amino acid residues that is at least 90% identical to an amino acid sequence as shown in SEQ ID NO:2 from amino acid 22-231 or 22-210, and wherein the soluble cytokine receptor polypeptide binds IL-TIF or antagonizes IL-TIF activity.

WEST

Generate Collection | Print

L14: Entry 5 of 9 File: EPAB Sep 12, 2002

DOCUMENT-IDENTIFIER: WO 2070655 A2
TITLE: MOUSE CYTOKINE RECEPTOR

Abstract (1):
Cytokine and their receptors have proven usefulness in both basic research, animal models, and as therapeutics. The present invention provides a new cytokine receptor designated as "mouse Zcytor16," which can bind and antagonize the IL-TIF cytokine.

L14: Entry 6 of 9 File: DWPI Sep 12, 2002

DERWENT-ACC-NO: 2002-698750
DERWENT-WEEK: 200275

TITLE: New Zcytor16 polypeptide useful for treating autoimmune or inflammatory diseases, e.g. inflammatory bowel disease, rheumatoid arthritis, asthma, atherosclerosis, cancer or diabetes, or in assessing therapeutic aspects of IL-TIF

Basic Abstract Text (24):
USE - The Zcytor16 polypeptide is useful in modulating the immune system by binding Zcytor16 ligand, and thus, preventing the binding of the ligand with endogenous Zcytor16 receptor. It is useful for studying human inflammation or immune function, or for treating autoimmune or inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, asthma, systemic lupus erythematosus, myasthenia gravis or allergy, atherosclerosis, cancer, diabetes, glomerulonephritis or pancreatitis, or in assessing therapeutic aspects of IL-TIF, chemical therapeutics, anti-IL-TIF antibodies, anti-Zcytor16 antibodies or Zcytor16 soluble receptors. The nucleic acid molecule and the anti-mouse Zcytor16 antibody are useful as probes in detecting gene expression and gene structure, such as in the diagnosis and/or prevention of spontaneous abortions or in monitoring placental health and function.

WEST

Generate Collection Print

L14: Entry 7 of 9 File: DWPI Feb 14, 2002

DERWENT-ACC-NO: 2002-217182
DERWENT-WEEK: 200244

TITLE: New soluble cytokine receptor which binds interleukin-T-cell inducible factor and antagonizes its activity in inflammatory and immune diseases such as cancer, diabetes, asthma, sepsis, psoriasis and autoimmune diseases

Basic Abstract Text (1):
NOVELTY - An isolated soluble cytokine receptor polypeptide (I), designated zcytor11 comprising a sequence (S1) of 211 amino acids defined in the specification or a sequence 90% identical to (S1) and which binds interleukin-T-cell inducible factor (IL-TIF) or antagonizes IL-TIF activity, where (I) forms homodimeric, heterodimeric or multimeric receptor complex, is new.

Basic Abstract Text (3):
(1) an isolated polynucleotide (II) that encodes (I), where the polypeptide encoded by the polynucleotide sequence binds or antagonizes IL-TIF having a sequence of 179 amino acids defined in the specification;

Basic Abstract Text (13):
MECHANISM OF ACTION - Antagonist of IL-TIF.

Basic Abstract Text (14):
USE - (I) is useful for reducing IL-TIF- or IL-9 induced inflammation, and inhibiting IL-TIF-induced proliferation of hematopoietic cells and their progenitors, especially lymphoid cells such as macrophages or T cells, by culturing bone marrow or peripheral blood cells with a composition comprising (I) to reduce proliferation of the hematopoietic cells in the bone marrow or peripheral blood cells as compared to bone marrow or peripheral blood cells cultured in the absence of soluble cytokine receptor. (I) is also useful for suppressing an immune response in a mammal exposed to an antigen or pathogen, by determining a level of an antigen- or pathogen-specific antibody, administering a composition comprising (I), determining a post administration level of antigen- or pathogen-specific antibody, and comparing the level of antibody before administration to the level of antibody after administration, where a lack of increase or a decrease in antibody level is indicative of suppressing an immune response. (I) is further useful for producing an antibody to soluble cytokine receptor polypeptide. (VI) is useful for producing a fusion protein (claimed). Soluble zcytor11 receptor or heterodimeric polypeptide is useful for enhancing the in vivo killing of target tissues by directly stimulating a zcytor11 receptor-modulated apoptotic pathway, resulting in cell death of hyperproliferative cells expressing zcytor11 receptor or a zcytor11 heterodimeric receptor, such as soluble zcytor11/CRF2-4 receptor. IL-TIF is involved in promoting Th1-type immune responses and antagonist of IL-TIF have beneficial use against diseases involving such immune responses. (I) is useful as cytokine antagonist and for detecting ligands that stimulate the proliferation and/or development of hematopoietic, lymphoid and myeloid cells in vitro and in vivo. Soluble zcytor11 heterodimers are useful as antagonists in inflammatory and immune diseases or conditions such as pancreatitis, type I diabetes (IDDM), pancreatic cancer, Graves disease, inflammatory bowel disease (IBD), Crohn's disease, colon and intestinal cancer, diverticulosis, autoimmune disease, sepsis, asthma, end-stage renal disease, psoriasis, organ or bone marrow transplant and kidney dysfunction. Soluble zcytor11 receptor or heterodimeric receptor polypeptides are useful in vivo or in diagnostic applications to detect IL-TIF expressing cancers in

vivo or in tissue samples and to prepare antibodies. Antibodies recognizing zcytoR11, soluble zcytoR11/CRF2-4 heterodimers, and multimers are useful to antagonize or agonize signaling by the IL-TIF receptors in the treatment of autoimmune disease such as IDDM, multiple sclerosis (MS), systemic lupus erythematosus (SLE), myasthenia gravis, rheumatoid arthritis and IBD. Anti-soluble zcytor11, anti-soluble zcytoR11/CRF2-4 heterodimer or multimer monoclonal antibody (MAb) is useful as an antagonist to deplete unwanted immune cells to treat autoimmune disease such asthma, allergy and other atopic disease. ZcytoR11 serves as a target for MAb therapy of cancer where an antagonizing MAb inhibits cancer growth and targets immune-mediated killing. Antibodies to soluble zcytor11 receptor or heterodimeric polypeptide are useful for tagging cells that express the corresponding receptors and assaying their expression levels, for affinity purification, within diagnostic assays for determining circulating levels of soluble receptor polypeptides, for detecting or quantitating soluble zcytor11 receptor or soluble zcytor11 heterodimeric polypeptide and as neutralizing antibodies or as antagonists to block zcytor11 receptor or zcytor11 heterodimeric polypeptide such as zcytor11/CRF2-4 or IL-TIF activity in vitro and in vivo.

L14: Entry 8 of 9 File: DWPI Feb 7, 2002

DERWENT-ACC-NO: 2002-195964
DERWENT-WEEK: 200238

TITLE: Stimulating expression of STAT transcription factor and inducing production of acute phase protein in a cell, involves contacting a cell capable of expressing STAT with T cell derived inducible factors

Basic Abstract Text (3):
(1) a method (M2) of modulating activity of an IL-TIF (IL is interleukin and TIF is T cell derived inducible factors), also knwon as IL-21, comprising contacting a cell susceptible to IL-TIF/IL-21 activity with an IL-TIF/IL-21 modulator, in an amount sufficient to modulate IL-TIF/IL-21 activity;

WEST

End of Result Set

Generate Collection | Print

L14: Entry 9 of 9 File: DWPI Jun 7, 2001

DERWENT-ACC-NO: 2001-356158
DERWENT-WEEK: 200270

TITLE: New soluble cytokine receptor polypeptides and polynucleotides, useful for diagnosing and treating cancer and inflammatory conditions

Basic Abstract Text (13):
(a) an aa sequence at least 90% identical to aa residues 22-231 or 22-210 of S1, where the polypeptide binds IL-TIF (undefined) or antagonizes IL-TIF activity; or

Basic Abstract Text (26):
(16) an isolated soluble cytokine receptor polypeptide (XIII) comprising an aa sequence at least 90% identical to a sequence of aa residues 22-231 or 22-210 of S1, where (XIII) binds IL-TIF (undefined) or antagonizes IL-TIF activity;

Basic Abstract Text (33):
MECHANISM OF ACTION - IL-TIF antagonist.

Basic Abstract Text (35):
(1) inhibiting IL-TIF induced proliferation or differentiation of hematopoietic cell(s) (progenitors);

Basic Abstract Text (36):
(2) reducing IL-TIF induced or IL-9 induced inflammation; and

Basic Abstract Text (39):
A polynucleotide comprising at least 14 contiguous nucleotides of S1 or its complement is useful for detecting a genetic abnormality and cancer in a patient (all claimed). Heteromeric/multimeric receptor polypeptides such as soluble zcytor 16/CRF2-4 can be used to reduce progression and symptoms of cancer. Zcytor16 polypeptides can also be used to detect IL-TIF levels which is indicative of pathological conditions including inflammatory states (e.g. rheumatoid arthritis) and cancer. Antibodies that bind zcytor16 polypeptides and the polypeptides themselves are useful for the treatment of inflammation, inflammatory diseases (e.g. infection, asthma, inflammatory bowel disease, rheumatoid arthritis and atherosclerosis) and autoimmune diseases.

Equivalent Abstract Text (13):
(a) an aa sequence at least 90% identical to aa residues 22-231 or 22-210 of S1, where the polypeptide binds IL-TIF (undefined) or antagonizes IL-TIF activity; or

Equivalent Abstract Text (26):
(16) an isolated soluble cytokine receptor polypeptide (XIII) comprising an aa sequence at least 90% identical to a sequence of aa residues 22-231 or 22-210 of S1, where (XIII) binds IL-TIF (undefined) or antagonizes IL-TIF activity;

Equivalent Abstract Text (33):
MECHANISM OF ACTION - IL-TIF antagonist.

Equivalent Abstract Text (35):
(1) inhibiting IL-TIF induced proliferation or differentiation of hematopoietic cell(s) (progenitors);

Equivalent Abstract Text (36):
(2) reducing IL-TIF induced or IL-9 induced inflammation; and

Equivalent Abstract Text (39):
A polynucleotide comprising at least 14 contiguous nucleotides of S1 or its complement is useful for detecting a genetic abnormality and cancer in a patient (all claimed). Heteromeric/multimeric receptor polypeptides such as soluble zcytor 16/CRF2-4 can be used to reduce progression and symptoms of cancer. Zcytor16 polypeptides can also be used to detect IL-TIF levels which is indicative of pathological conditions including inflammatory states (e.g. rheumatoid arthritis) and cancer. Antibodies that bind zcytor16 polypeptides and the polypeptides themselves are useful for the treatment of inflammation, inflammatory diseases (e.g. infection, asthma, inflammatory bowel disease, rheumatoid arthritis and atherosclerosis) and autoimmune diseases.

WEST

Generate Collection Print

L14: Entry 2 of 9 File: PGPB Aug 1, 2002

PGPUB-DOCUMENT-NUMBER: 20020102723
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020102723 A1

TITLE: Interleukin-22 polypeptides, nucleic acids encoding the same and methods for the treatment of pancreatic disorders

PUBLICATION-DATE: August 1, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gurney, Austin L.	Belmont	CA	US	
Aggarwal, Sudeepta	San Bruno	CA	US	
Xie, Ming-Hong	San Francisco	CA	US	
Maruoka, Ellen M.	San Francisco	CA	US	
Foster, Jessica S.	Hayward	CA	US	
Goddard, Audrey	San Francisco	CA	US	
Wood, William I.	Hillsborough	CA	US	

US-CL-CURRENT: 435/320.1; 424/134.1, 435/325, 435/69.1, 514/44, 530/324, 530/350, 530/387.9, 536/23.5

CLAIMS:

What is claimed is:

1. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence that encodes (a) amino acids 1-179 of SEQ ID NO: 2, or (b) amino acids X- 179 wherein X is any amino acid from 29-38 of (SEQ ID NO:2), or the compliment thereof.

2. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence shown in FIG. 1 (SEQ ID NO: 1), or the compliment thereof.

3. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence of the full-length coding sequence shown in FIG. 1 (SEQ ID NO: 1), or the compliment thereof.

4. Isolated nucleic acid having at least 80% nucleic acid sequence identity to the full-length coding sequence of the DNA deposited under ATCC accession number PTA-1031, on December 7, 1999, or the compliment thereof.

5. Isolated nucleic acid 1152 nucleotides long as shown in SEQ ID NO: 1, and the compliment thereof.

6. A vector comprising the nucleic acid of claim 1.

7. The vector of claim 6, operably linked to control sequences recognized by a host cell transformed with the vector.

8. A host cell comprising the vector of claim 7.

9. The host cell of claim 8, wherein said cell is a CHO cell, an E. coli bacterium or a yeast cell.

10. Aprocess for producing an IL-22 polypeptides comprising culturing the host cell of claim 8 under conditions suitable for expression of said IL-22 polypeptide and recovering said IL-22 polypeptide from the cell culture.

11. An isolated polypeptide having at least 80% amino acid sequence identity to the amino acid sequence shown in FIG. 2 (SEQ ID NO:2),or the amino acid sequence shown in FIG. 2 (SEQ ID NO:2), lacking amino acids 1 to about 33.

12. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence encoded by the full-length coding sequence of the DNA deposited under ATCC accession number PTA-1031, on Dec. 7, 1999.

13. A chimeric molecule comprising a polypeptide according to claim 12 fused to a heterologous amino acid sequence.

14. The chimeric molecule of claim 13, wherein said heterologous amino acid sequence is an epitope tag sequence.

15. The chimeric molecule of claim 14, wherein said heterologous amino acid sequence is a Fc region of an immunoglobulin.

16. An antibody which binds to a polypeptide according to claim 11.

17. The antibody of claim 16, wherein said antibody is a monoclonal antibody, a humanized antibody or a single-chain antibody.

18. The antibody of claim 15, wherein said antibody blocks the binding of IL-22 to a receptor.

19. A method for inhibiting IL-22 induced expression of PAP1 by pancreatic cells in a system comprising said cells, said method comprising contacting said system with an IL-22 antagonist, thereby inhibiting said PAP1 expression by said pancreatic cells.

20. The method of claim 19, wherein said antagonist is anti-IL-22 antibody.

21. The method of claim 19, wherein said antagonist is IL-22 antisense nucleic acid.

22. The method of claim 19, wherein step of contacting occurs in vitro.

23. A method of treating a pancreatic disorder in a mammal, comprising administering to said mammal, an effective amount of an IL-22 antagonist.

24. The method of claim 23, wherein the pancreatic disorder is acute pancreatitis, chronic pancreatitis, pancreatic carcinoma, including acinar cell carcinoma or mixed cell population pancreatic carcinoma.

25. A method of reducing the activated or inflamed condition of the pancreas in a mammal, comprising administering to said mammal an effective amount of an IL-22 antagonist.

26. The method of claim 25 wherein said antagonist is an anti-IL-22 antibody.

27. The method of claim 25 wherein said antagonist is an IL-22 antisense nucleic acid.

28. A method ofreducing the activated or inflamed condition of the pancreas in a mammal, comprising administering to said mammal an effective amount of an IL-22R/IL-10RP complex antagonist, antagonist antibody, or a fragment thereof that inhibits IL-22 polypeptide binding.

29. A method for preventing the onset of a pancreatic disorder in a mammal, comprising administering to said mammal an effective amount of an IL-22R/IL-10R.beta. complex

antagonist.

30. The method of claim 29. wherein said antagonist is an antagonist antibody.

31. The method of claim 29 wherein said antagonist is an antibody fragment.

32. A method of diagnosing the activated or inflammatory state of the pancreas in a mammal, comprising contacting a biological sample obtained from the pancreas of said mammal with IL-22 and measuring STAT3 polypeptide supershift, wherein the presence of the supershift is indicative of the presence of said disorder.

33. A method of identifying a compound that inhibits the expression of a gene encoding IL-22 polypeptide, said method comprising contacting cells which normally express said IL-22 polypeptide with a candidate compound, and determining the lack of expression of said gene.

34. The method of claim 33, wherein said candidate compound comprises an IL-22 antisense nucleic acid.

35. An article of manufacture, comprising: a container; a label on the container; and a composition comprising an active agent contained within the container; wherein the composition is effective for reducing either acute or chronic pancreatitis in a mammnal, the label on the container indicates that the composition can be used for treating a pancreatic disorder, and the active agent in the composition is an agent inhibiting the activity or expression of an IL-22 polypeptide.

36. A method of detecting IL-22 polypeptide in a sample suspected of containing an IL-22 polypeptide, said method comprising contacting said sample with an IL-10R.beta. polypeptide (SEQ ID NO: 3) or an IL-22R polypeptide (SEQ ID NO: 4) and determining the formation of a IL-22/IL-10R.beta. polypeptide conjugate or a IL-22/IL-22R polypeptide conjugate in said sample, wherein the formation of a conjugate is indicative of the presence of an IL-22 polypeptide in said sample.

37. The method according to claim 36, wherein said sample comprises cells suspected of expressing said IL-22 polypeptide.

38. The method according to claim 36, wherein said IL-10R.beta. polypeptide is labeled with a detectable label or is attached to a solid support.

39. The method according to claim 36, wherein said IL-22R polypeptide is labeled with a detectable label or is attached to a solid support.

40. A method of detecting an IL-22R polypeptide or an IL-10R.beta. polypeptide in a sample suspected ofcontaining an IL-22R polypeptide or an IL-10R.beta. polypeptide, said method comprising contacting said sample with an IL-22 polypeptide and determining the formation of an IL-22R/IL-22 polypeptide conjugate or an IL-10R.beta./IL-22 polypeptide conjugate in said sample, wherein the formation of a conjugate is indicative of the presence of an IL-22R polypeptide or IL-10R.beta. polypeptide in said sample.

41. The method according to claim 40, wherein said sample comprises cells suspected of expressing an IL-22R polypeptide or an IL-100R.beta. polypeptide.

42. The method according to claim 40, wherein said IL-22 polypeptide is labeled with a detectable label or attached to a solid support.

43. A method of linking a bioactive molecule to a cell expressing an IL-22 polypeptide, said method comprising contacting said cell with an IL-22R polypeptide or an IL-10R.beta. polypeptide that is bound to said bioactive BOO molecule and allowing binding of said IL-22 polypeptide and said IL-22R polypeptide or said IL-22 polypeptide and said IL-10R.beta. polypeptide, thereby linking said bioactive molecules to said cell

44. The method according to claim 43, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.

45. The method recording to claim 43, wherein said bioactive molecule causes the death of said cell.

46. A method of linking a bioactive molecule to a cell expressing IL-22R polypeptide or IL-10R.beta. polypeptide said method comprising contacting said cell with an IL-22 polypeptide that is bound to said bioactive molecule and allowing binding of said IL-22 polypeptide and said IL-22R or said IL-22 polypeptide and the IL-10R.beta. polypeptide, thereby linking said bioactive molecules to said cell.

47. The method according to claim 46, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.

48. The method according to claim 47, wherein said bioactive molecule causes the death of said cell.

49. A method of modulating at least one biological activity of a cell expressing an IL-22 polypeptide, said method comprising contacting said cell with (a) an IL-22 R polypeptide, (b) an IL-10R.beta. polypeptide or (c) an anti-IL-22 polypeptide antibody, whereby said (a) IL-22 R polypeptide, (b) IL-10R.beta. polypeptide or (c) anti-IL-22 polypeptide antibody binds to said IL-22 polypeptide, thereby modulating at least one biological activity of said cell.

50. The method according to claim 49, wherein said cell is killed.

51. A method of modulating at least one biological activity of a cell expressing IL-22R polypeptide or IL-10R.beta. polypeptide wherein, said method comprising contacting said cell with (a) an IL-22 polypeptide, (b) an anti-IL-22R polypeptide antibody or (c)an anti-IL-10R.beta. polypeptide antibody, whereby said (a) IL-22 polypeptide, (b) anti-IL-22R polypeptide antibody or (c) anti-IL-10R.beta. polypeptide antibody binds to said IL-22R polypeptide or IL-10R.beta. polypeptide, thereby modulating at least one biological activity of said cell.

52. The method according to claim 51, wherein said cell is killed.

WEST

End of Result Set

☐ Generate Collection | Print

L12: Entry 1 of 1 File: PGPB Jul 4, 2002

DOCUMENT-IDENTIFIER: US 20020085992 A1
TITLE: Method for treating inflammation

Summary of Invention Paragraph (31):
[0030] A receptor has been discovered that binds to both IL-19 and mda7 and is a heterodimer comprised of the polypeptide termed `interleukin-20 receptor alpha IL-20RA` and a polypeptide termed interleukin-20 receptor beta `IL-20RB`. The IL-20RA polypeptide, nucleic acid that encodes it, antibodies to IL-20RA and methods for producing it are disclosed in U.S. Pat. No. 5,945,511 issued Aug. 31, 1999. SEQ ID NOs: 1-3 are the polynucleotides and polypeptides of IL-20RA. The mature extracellular sequence of IL-20RA is comprised of SEQ ID NO: 3. The IL-20RB polypeptide, nucleic acid that encodes it, antibodies to IL-20RB and methods for producing it are disclosed in International Patent Application No. PCT/US99/03735 (publication no. WO 99/46379) filed on Mar. 8, 1999. A variant of IL-20RB (hereinafter referred to as V-IL-20RB has been cloned and is defined by SEQ ID NOs: 4-6, SEQ ID NO: 6 being the extracellular domain.

L14: Entry 1 of 9 File: PGPB Oct 24, 2002

DOCUMENT-IDENTIFIER: US 20020156013 A1
TITLE: Asthma associated factors as targets for treating atopic allergies including asthma and related disorders

Detail Description Paragraph (87):
[0132] One of several cDNA identified from the difference analysis was found to be a novel cDNA. A full-length cDNA was cloned from a murine cDNA library using the fragment isolated as a probe. A TS2 cDNA library was prepared by conventional methods in the pSVK3 plasmid library as previously described (Louahed et al., 1995). A 1119 bp cDNA was isolated which contained an open reading frame encoding for a protein of 208 amino acids which is M-Ras. FIG. 1 shows the nucleotide and amino acid sequence of the M-Ras cDNA. A nucleotide BLAST (Altschul et al., 1990) database search of the full length cDNA revealed it to be similar to several Ras proteins. FIG. 2 shows an alignment of M-Ras to H-Ras and R-Ras proteins. Motif analysis of the encoded polypeptide shows several features such as a nucleotide binding domain in the N-terminus and a CAAX motif at the C-terminus. These are hallmark features of other Ras protein members and suggests that M-Ras is an IL-9 inducible gene involved in signal transduction.

Detail Description Paragraph (95):
[0136] RT-PCR analysis of RNA derived from the tissues of the IL-9 transgenic (Tg5) and the parental strain (FVB) revealed that both strains expressed M-Ras in the kidney, lung and brain (FIG. 4). This data demonstrates that the IL-9 inducible gene M-Ras is expressed in several tissues in mice including the lung. This data also suggests that M-Ras may play a role in the physiology of these organs.

L14: Entry 2 of 9 File: PGPB Aug 1, 2002

DOCUMENT-IDENTIFIER: US 20020102723 A1
TITLE: Interleukin-22 polypeptides, nucleic acids encoding the same and methods for the treatment of pancreatic disorders

Summary of Invention Paragraph (8):
[0006] Interleukin-22 (IL-22) is a newly identified cytokine produced by activated T cells and is related to interleukin-10 (IL-10). IL-22 signals through a receptor complex comprised of CRF2-4, also known as IL-10R.beta., and a new member of the class II cytokine receptor family, interleukin-22 receptor (IL-22R) [Xie et al., J. Biol. Chem. (2000) 275, 31335-31339]. Of the members of this receptor complex, IL-10R.beta. is expressed in several tissues while the expression of IL-22R is fairly restricted,with high expression in the pancreas, suggesting that IL-22R is controlling the site of action of IL-22. As an example, murine IL-22 induces changes in gene expression in pancreatic acinar cells of several genes including pancreatitis associated protein (PAP1), a gene overexpressed in acute pancreatitis [Iovanna et al, J. Biol. Chem. (1991) 266, 24664-246691. IL-22 signaling through a receptor complex that is highly expressed in pancreas, suggests that IL-22 may modulate an immune/inflammatory response in the pancreas, and may be involved in diseases of the pancreas including pancreatitis.

Brief Description of Drawings Paragraph (4):
[0027] FIG. 3 shows Northern Blots probed with an interleukin-22 receptor probe.

Brief Description of Drawings Paragraph (5):
[0028] FIG. 4 shows the expression of interleukin-22 receptor RNA from various human tissues as analyzed by Taqman.TM. analysis.

Detail Description Paragraph (253):
[0279] The results of this are shown in FIG. 4. Interleukin-22 receptor was expressed highest in pancreas, with expression detected in fetal liver, adult liver, kidney, intestine and colon.

L14: Entry 3 of 9 File: PGPB Apr 4, 2002

DOCUMENT-IDENTIFIER: US 20020039763 A1
TITLE: Interferon-like protein Zcyto21

Summary of Invention Paragraph (8):
[0008] IL-22, also known as IL-TIF (IL-10-related T cell-derived inducible factor) (Dumoutier et al., J. Immunology 164, 1814-1819, (2000)), is a recently described IL-10 homologue. Mouse IL-22 was originally identified as a gene induced by IL-9 in T cells and mast cells in vitro (Dumoutier et al., J. Immunology 164, 1814-1819, (2000)). Acute phase reactant induction activity was observed in mouse liver upon IL-22 injection, and IL-22 expression was rapidly induced after lipopolysaccharide (LPS) injection, suggesting that IL-22 contributes to the inflammatory response in vivo (Dumoutier et al., Proc. Natl. Acad. Sci. U.S.A. 97, 10144-10149, (2000)).

WEST

Help | Logout | Interrupt

Main Menu | Search Form | Posting Counts | Show S Numbers | Edit S Numbers | Preferences | Cases

Search Results -

Term	Documents
(12 AND 14).USPT,PGPB,JPAB,EPAB,DWPI,TDBD.	0
(L14 AND L12).USPT,PGPB,JPAB,EPAB,DWPI,TDBD.	0

Database:
US Patents Full-Text Database
US Pre-Grant Publication Full-Text Database
JPO Abstracts Database
EPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L15

Refine Search

Recall Text | Clear

Search History

DATE: Friday, December 27, 2002 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=ADJ			
L15	L14 and l12	0	L15
L14	interleukin-22 receptor or interleukin 22 receptor or il-9 inducible gene or il-tif or il-10 related t cell derived inducible factor	9	L14
L13	il-22 receptor	6	L13
L12	interleukin-20 receptor beta or il-20r-beta	1	L12
L11	l5 and (interleukin-20 receptor beta or il-20rbeta)	0	L11
L10	l5 and (interleukin-20 receptor beta or il-20r-beta)	0	L10
L9	l5 and (interleukin-20 receptor beta or il-20beta receptor)	0	L9
L8	l5 and interleukin-20 receptor beta or il-20r-beta	0	L8
L7	l5 and interleukin-20 receptor beta or il-20rbeta	0	L7
L6	l5 and (interleukin-22 receptor or interleukin 22 receptor or il-9 inducible gene or il-tif or il-10 related t cell derived inducible factor)	1	L6
L5	l3 or l4	29	L5
L4	L3 and l2	5	L4
L3	renauld-jean-christophe.in.	29	L3
L2	dumoutier-laure.in.	5	L2
L1	domoutier-laure.in.	0	L1

END OF SEARCH HISTORY